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Cue reactivity as a predictor of successful abstinence initiation among adult smokers

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Abstract

The association between smokers' cue-induced craving and subsequent ability to initiate abstinence is unclear. Dependent smokers (N=158) completed a single cue-reactivity session prior to participating in a larger within-subjects study, which independently examined predictors of initiating quitting during 5 days each on nicotine versus placebo patch. In the larger study, all smokers used nicotine and placebo patch (double blind) for one week each following a preceding week of ad lib smoking, in a 2x2 cross-over design. Generalized estimating equation (GEE) models determined the predictive ability of cue-induced craving (cue reactivity) on subsequent success at initiating a quit attempt (at least 24hrs quit) for each patch condition. Smokers who exhibited greater craving during exposure to smoking cues had significantly greater odds of successfully initiating abstinence during either quit attempt week (i.e., the nicotine or placebo patch week). This relationship was not statistically significant for self-reported craving in response to neutral cues. However, a greater smoking-neutral cue difference score for cue-induced craving was also a significant predictor successfully initiating abstinence, but only among those not monetarily reinforced. Implications of these seemingly counterintuitive findings are discussed.

Keywords

Predictors; Relapse; Cue reactivity; Abstinence initiation; Smoking cessation

Cue-induced reactivity among smokers, in which increased urge to smoke is brought on by exposure to smoking-related stimuli, is a well-established phenomenon in human addiction laboratories (see Carter & Tiffany, 1999). Most commonly, cue reactivity involves examining changes in subjective (e.g., craving), physiological (e.g., heart rate), and/or, less commonly, behavioral (e.g., latency to smoke) responding brought on by a smoker's exposure to smoking-related cues (e.g., lit cigarettes) compared to neutral cues (e.g., pad of paper). Although this type of cue-specific responding has been repeatedly and reliably demonstrated, considerable debate has arisen regarding the utility of cue-reactivity smoking research to elucidate other important aspects of nicotine dependence (Perkins, 2009; Shiffman 2009, Tiffany, 2009). Specifically, the clinical implications of this cue-reactivity phenomenon have not been well studied. Thus, little is known about the relationship between cue responding and a smoker's likelihood of quitting and/or probability of relapsing.

One of the main assumptions of smoking cue-reactivity research is that greater responding to cues should be negatively associated with smoking cessation success (e.g., Drummond, 2000.) Although some support for this notion has been found in studies examining physiological reactivity (e.g., Niaura et al., 1988), very little support has been shown for the relationship between self-reported craving, the most commonly studied measure of reactivity, and smoking outcome measures. In fact, in all but one trial no evidence of a link between heightened cue-induced craving and better abstinence outcome has been revealed

(see Perkins, 2012); and, in that one positive study the relationship was found only among individuals medicated with the nicotine patch (Waters et al. 2004). Thus, evidence in support of a predictive relationship between heightened cue-induced reactivity and cigarette use is very limited.

Somewhat surprisingly, the opposite has also been found. That is, heightened cue-induced craving has been associated with *increased* ability to quit. For example, in a 1999 study on smoking cue-extinction treatment, Niaura and colleagues found that the only variable predictive of time to relapse to smoking was the total number of cue exposure sessions during which an individual's craving *increased* or stayed the same. Such cue-induced craving predicted a longer time to lapse over the following 12 months, as well as greater likelihood of being abstinent at both 6 and 12 month follow-up (Niaura et al., 1999). More recently, Powell et al., (2011) found that heightened pre-quit cue-induced craving was inversely related to relapse risk. Thus, it may be the case that cue-induced craving does not index the difficulty smokers will have refraining when exposed to smoking cues during a quit attempt, but rather taps some motivational process or cognitive awareness that enables them to remain quit.

The purpose of the present investigation was to examine whether cue-induced self-report craving predicted a smoker's ability to initiate a brief quit attempt, and, if so, to determine the directionality of that relationship. We assessed smokers' reactivity to smoking cues and neutral cues, as well as the difference score between them (smoking cue minus neutral cue craving), as predictors of smoking abstinence initiation.

Method

Participants

One hundred and sixty two participants (77 male, 85 female) completed a 1-hour cue-reactivity session. Individuals were on average 29.9 years old (range 18–61), smoked 17.19 cigarettes per day (range 10–42), had an average Fagerstrom Test of Nicotine Dependence (FTND) (Heatherton et al. 1991) score of 4.7, and an average CO of 23.6 (range 8–53). One participant was excluded prior to analysis for failure to follow directions, three were excluded for unresponsiveness to cues (i.e. craving response to smoking cues minus response to neutral cues < 0), leaving 158 (40.3% were high in quit interest; 54.6% were monetarily reinforced) for the present analyses.

All participants completed the independent cue-reactivity session prior to participating in a larger study (Perkins et al., 2008) which examined predictors of short term ability to quit while on nicotine versus placebo patch. For that study, smokers attempted to quit on two occasions, during two 5-day periods while using either nicotine or placebo patch (double blind), each preceded by a week of ad lib smoking. As part of that within subject 2x2 crossover design, smokers were recruited based on whether they had either high quit interest (i.e. interested in quitting within the next month) or low quit interest (not interested in quitting within the next 6 months). Also, the study design compared those who either received monetary reinforcement for quitting (\$12/day) or did not. These study methods are described in more detail elsewhere (Perkins et al., 2008).

Procedures

After signing consent forms, a CO measure was taken using a Vitalograph CO monitor (Vitalograph; Lenexa, KS). Participants who met the >8ppm CO cutoff, which confirmed they were currently smoking, were instructed to light a cigarette and take at least one puff to ensure baseline smoking satiation. This was done to equate time since last nicotine exposure in an effort to reduce artificially inflating cue-induced craving due to withdrawal (Tiffany et

al. 2009). They then completed a smoking history form, and the FTND. Participants were given instructions for the remainder of the computer-automated cue-reactivity session and underwent a neutral practice trial to verify that they understood the procedure.

The experimenter then left the room and participants completed 12 trials (6 pictorial smoking cues, 6 pictorial neutral cues in a non-blocked counterbalanced order such that no cue type occurred more than twice in a row). Stimuli included pictures of objects and places developed in our past studies and demonstrated to be strongly associated with smoking (e.g., lit cigarette, a bar) or to be neutral with regard to smoking (e.g., a pen and pad, a church; Conklin et al., 2008). The automated presentation of each picture on a large computer screen followed a standard format: 20 seconds relaxation, 20 seconds baseline, during which they sat quietly, 40 seconds picture viewing, during which they focused intently on 4 angles of the same object or place for 10 seconds each, and post-trial subjective rating period, during which they rated the vividness of the stimuli, their level of cue-elicited craving (QSU-4, Carter & Tiffany, 2001), negative affect, and positive affect (Deiner & Emmons, 1984). All ratings were done on a 0–100 scale.

Within 7 days subjects participated in the main study (Perkins et al., 2008), consisting of 4 weeks of intermittent clinic visits while ad lib smoking (weeks 1 and 3) or while attempting to quit while on nicotine (21 mg) or placebo patch (weeks 2 and 4, in a counterbalanced order across subjects). Regardless of treatment-interest status, all subjects promised in writing that they would try hard to quit during the week of each patch condition. Abstinence during both practice quit attempt weeks was verified daily (Mon-Fri) by expired-air CO < 5 ppm and self-report of no smoking at all to ensure complete abstinence over the prior 24 hrs (Javors, Hatch, & Lamb, 2005). Other details of the larger study are described elsewhere (Perkins et al. 2008).

Data Coding and Analysis

An initial pairwise comparison of self-reported craving to the smoking and neutral cues was conducted to ensure that a significant cue-reactivity effect was achieved. Quit data from the larger study was coded 0 (did not initiate a quit attempt) or 1 (did initiate a quit attempt) to indicate whether or not each participant successfully quit smoking for at least 24-hours during the week-long practice quit attempt under either the nicotine or placebo patch conditions (or both).

To examine the relationship between self-reported craving in response to cues and ability to initiate a quit attempt, GEE models assuming the binomial distribution and the logit link were employed. GEE models account for the correlation of repeated measurements on the same subject in the crossover design. Three models were developed, one to test the predictive ability of craving in response to smoking cues, another to test craving in response to neutral cues, and a third to examine the smoking-neutral craving difference score as a predictor. (Note: Baseline craving was low due to smoking satiation prior to cue reactivity and was the same for each cue condition, as this was a within-subjects test; therefore, no baseline correction is needed for any analyses.) Each model contained the between-subjects factors of high/low quit interest and monetary/no reinforcement, and the within-subjects factors of treatment (nicotine or placebo patch) and period (week). Additional covariates included age, sex, FTND, and cigarettes smoked per a day (CPD). Each covariate was assessed for significance and confounding. Only covariates with $p < .05$ or with a confounding effect on the estimate of craving scores were retained in the final model. Additionally, interactions between craving and the between- and within-subjects factors were examined and retained if $p < .05$. The interaction for crossover effect was also assessed. All analyses were performed using SAS v.9.2 (SAS Institute Inc, Cary, NC).

Results

The initial pairwise t-test on craving to smoking cues versus neutral cues revealed a very large significant difference, $t(157) = 19.20$ $p < .0001$, as smoking cues induced much greater craving, $m = 44.55$ (SD: 25.61) compared to neutral cues $m = 13.50$ (SD: 14.57), as expected. The effect size for this difference was $d = 1.75$, considered large according to Cohen (1988). The mean cue reactivity score was 31.05 (SD: 20.29).

The final GEE models included treatment seeking status, monetary reinforcement, treatment, period and CPD as covariates and either craving to smoking cues, craving to neutral cues, or the craving to smoking-neutral cue difference as the primary predictor of interest. Age, sex, and FTND were excluded from the model based on nonsignificance ($p > .05$). There were no interactions with craving measures and no crossover effect was observed (i.e. order of patch conditions). However, an interaction between monetary reinforcement and cue reactivity occurred. All models fit adequately as evidenced by plots for goodness of fit. Table 1 provides the model estimates and p-values for all 3 models. As anticipated, initiation of a quit attempt for at least 24 hr in all participants was achieved by 46.0% during the placebo patch week and by 59.6% during the nicotine patch week.

Results of the model on smoking cue craving revealed that cue-induced craving following smoking cues was associated with a higher probability of initiating a quit attempt. For example, for a 10 pt increase in craving, the log odds of initiating a quit attempt increased by .147 (OR(95%CI): 1.16(1.02–1.31)), suggesting the odds of initiating a quit attempt are 15.8% higher for a smoking cue craving score of 50 compared to a craving score of 40 (See Figure 1). In the second model, neutral cues were in the same direction but were not a significant predictor of quit initiation (see Table 1b).

Unexpectedly, the smoking-neutral cue craving difference model indicated an interaction between cue reactivity and monetary reinforcement for quitting ($p = .037$; See Figure 2). For nonreinforced participants, as a smoker's difference score between cue-induced craving to smoking cues minus neutral cues increased, the log odds of quit initiation also increased (β (SE) = .0354 (.014)). Therefore, a nonreinforced participant with a cue reactivity difference score of 50 compared to a nonreinforced participant with a difference score of 40 had a .354 (OR(95%CI): 1.42(1.09–1.87)) increase in the log odds of quit initiation, or a 42.5% increase in the odds of initiating a quit attempt. This relationship is similar to that found with the model examining smoking cues independent of neutral cues above. However, monetary reinforcement attenuated the relationship of cue reactivity with quit initiation, as a reinforced participant with a cue reactivity difference score of 50 compared to a reinforced subject with a difference score of 40 had approximately equal odds of initiating a quit attempt. The interaction between cue reactivity difference score and quit interest approached significance ($p = .063$) prior to removal from the model.

Regarding the other factors included in the three models, monetary reinforcement and being on nicotine patch treatment were both significant predictors of the likelihood of initiating a quit attempt, consistent with previously reported findings (Perkins et al. 2008). Treatment interest status and CPD were not associated with the likelihood of initiating a quit attempt in any model. See Table 1 for model estimates and p-values.

Discussion

This analysis offers preliminary support for the utility of smoking cue-induced self-report craving to predict a smoker's ability to initiate abstinence during a short-term simulated quit attempt, but may do so in a manner opposite of that often expected. Namely, smokers reporting *greater* craving in response to smoking cues had a *higher* probability of

successfully initiating a short-term quit attempt. This was true when smoking cue-induced craving was examined as the predictor, as well as for the cue-induced craving difference between reactivity to smoking cues minus neutral cues. Although in the same direction, this relationship was not significant for reactivity to neutral cues alone. However, when subjects were monetarily reinforced for quitting, cue reactivity was not a predictor of abstinence initiation. Thus, reinforcement for quitting may override the association of cue reactivity with abstinence initiation. As a whole, these results suggest that among smokers not monetarily reinforced for quitting, as smoking cue craving increases, or as the difference between smoking and neutral cues increases, so too does the likelihood of successfully initiating abstinence.

These findings stand in sharp contrast to the supposition that a smoker who experiences greater cue-induced craving should have a harder time quitting. Yet, there is more indirect support than not in the direction of the result found. As mentioned above, Niaura et al (1999) found that the number of sessions during which cue-induced craving increased or stayed the same during cue exposure predicted a longer time to relapse among smokers. More recently, Powell et al., (2011) found that smokers with greater pre-quit cue reactivity, indexed as smoking cue (cigarette) minus neutral cue (scotch tape) craving response, were less likely to relapse to smoking at follow-up. Additionally, other indices of cue responding may show findings of similar directionality with regard to cessation prediction. In an MRI study, McClernon et al. (2007) found greater pre-treatment activation in the thalamus and ventral striatum as a function of smoking cues among individuals who went on to successfully abstain from smoking.

As a consequence, cue reactivity may reflect active cognitive processes at work in preparation for attempting abstinence among those who actually truly intend to do so. Their heightened awareness of the saliency of smoking-related cues may reflect effortful processing of their intention to refrain from smoking (Tiffany, 1990). In fact, cognitive processes reflecting attentional biases for smoking-related words (e.g., modified Stroop task) have been shown to be related to cessation outcomes in smokers (Waters et. al., 2003). Similarly, the Theory of Ironic Processing (Wegner, 1992, 1994) states that an individual's deliberate attempt to suppress or avoid specific thoughts results in those thoughts being even more persistent. Perhaps individuals who truly intend to make a quit attempt try to avoid thinking about smoking and related stimuli in preparation for cessation. According to the theory, this attempt at thought suppression could lead to the opposite effect, making the target cognitions even more prominent in the individual's mind. Consistent with this idea, limbic activation during magnetic resonance imaging was greater when smokers were told to "resist" craving a cigarette, rather than to actively crave the cigarette (Brody, Mandelkern, Olmstead, Jou, Tjongson, Allen, et al., 2007).

Although the positive relationship between reactivity to smoking cues, as well as the smoking cue-neutral cue difference score, and abstinence initiation was clear, there was also a trend towards increased craving to neutral cues being associated with successful initiation as well. When using standard cues, some neutral cues may be associated with smoking for some smokers (See Table 1). Alternatively, it may be the case that smokers who truly intend to attempt abstinence demonstrate nonspecific enhanced craving to cues. Further research is needed to parse out the relationship between craving during neutral stimuli and smoking-related outcomes.

Although not surprising, the predictive validity of the smoking-neutral craving difference score on abstinence initiation disappeared when smokers were monetarily reinforced for quitting. Numerous studies have shown that monetary reinforcement robustly increases abstinence initiation among smokers (e.g., Gilbert, Crauthers, Mooney, McClernon, &

Jensen, 1999, Sweitzer, Denlinger, & Donny, 2012). The strength of that relationship likely masks the relationship between cue responding and quit initiation. Therefore, it is important that future studies examining the predictive value of cue reactivity on quitting be done in the absence of monetary reinforcement. Such studies would allow the relationship to be more clearly revealed.

One limitation of the present study is that it is an analogue study, not an actual smoking cessation trial. However, there is evidence that the majority of smokers' quit attempts are unplanned and/or opportunistic (Ferguson, Shiffman, Gitchell, Sembower, & West, 2009; Larabie, 2005). Thus, the present results, especially in the non-reinforced subjects, may generalize well to real world quitting situations. Additionally, we assessed quit initiation, but not quit persistence, although initiation is a step the majority of smokers will revisit numerous times before successfully achieving long-term abstinence (Hughes, 1999; Hymowitz, 1997). Still, more direct tests of the relationship between cue reactivity and outcome measures of smoking are needed. Specifically, pre- and post-treatment cue reactivity with smokers could directly inform the validity of cue reactivity to predict cessation success or failure. Better understanding of how cue exposure affects smoking behavior regardless of an individual's treatment status would greatly enhance the clinical relevance and utility of cue reactivity research for understanding nicotine dependence.

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Figure 1.
Log odds of abstinence initiation per a 10 unit increase in craving to smoking cues.

Figure 2.

Log odds of abstinence initiation per a 10 unit increase in smoking-neutral cue-induced craving difference score, by those monetarily reinforced or not reinforced for abstinence.

Table 1

(A) Smoking Cue Model						
Effect	Estimate	Std. Err.	95% Confidence Limits			p-value
Intercept	-0.584	0.617	-1.794	0.626		0.344
Quit Interest	-0.237	0.322	-0.868	0.395		0.463
Monetary Reinforcement	1.777	0.329	1.133	2.422		<.0001
Period	-0.277	0.176	-0.621	0.068		0.116
Patch Treatment	0.665	0.179	0.313	1.017		<.0001
CPD	-0.061	0.036	-0.132	0.010		0.094
Craving--Smoking Cues	0.015	0.006	0.002	0.027		0.020
(B) Neutral Cue Model						
Effect	Estimate	Std. Err.	95% Confidence Limits			p-value
Intercept	-0.138	0.606	-1.325	1.049		0.819
Quit Interest	-0.180	0.323	-0.813	0.452		0.576
Monetary Reinforcement	1.789	0.327	1.149	2.430		<.0001
Period	-0.269	0.174	-0.610	0.072		0.122
Patch Treatment	0.654	0.176	0.308	1.000		<.0001
CPD	-0.065	0.036	-0.137	0.006		0.073
Craving--Neutral Cues	0.019	0.012	-0.004	0.041		0.105
(C) Smoking-Neutral difference score Model						
Effect	Estimate	Std. Err.	95% Confidence Limits			p-value
Intercept	-1.295	0.697	-2.660	0.070		0.063
Quit Interest	-0.115	0.333	-0.767	0.537		0.729
Monetary Reinforcement	2.909	0.672	1.591	4.227		<.0001
Period	-0.294	0.178	-0.644	0.055		0.099
Patch Treatment	0.680	0.181	0.325	1.035		<.0001
CPD	-0.051	0.037	-0.122	0.021		0.166

(C) Smoking-Neutral difference score Model						
Effect	Estimate	Std. Err.	95% Confidence Limits		p-value	
			Lower Bound	Upper Bound		
Craving-difference score	0.035	0.014	0.008	0.063	0.011	
Craving-difference score x Monetary reinforcement	-0.035	0.017	-0.068	-0.002	0.037	